

Paracetamol Research and New Formulation Design

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Abstract: Acetaminophen, also known as paracetamol, is the main metabolite of phenacetin and is a derivative of acetanilide. It is a commonly used antipyretic and analgesic drug. Acetaminophen is rapidly and completely absorbed orally in body fluids. Evenly distributed in the medium, but inappropriate doses can lead to serious side effects - liver toxicity. With the development of technology, 3D printing technology shows great potential in personalized drug delivery. It can not only print medicines with different doses quickly and conveniently, but also design integrated tablets with multiple independent release mechanisms according to the needs of patients. This paper aims to use 3D printing technology to solve the problem of side effects caused by individual differences, so as to prepare safe, effective and personalized pharmaceutical preparations.

Keywords: Paracetamol, Acetaminophen, 3D printing technology, Hot melt extrusion.

1. Introduction

Paracetamol, also known as Tylenol, Panadol, Bufferin, is the metabolite of phenacetin the body. Paracetamol/acetaminophen is one of the most popular and most commonly used analgesic and antipyretic drugs around the world, available without a prescription, both in mono- and multi-component preparations. During the inflammatory reaction, the arachidonic acid of the tissue cells synthesizes prostaglandins and other inflammatory mediators through cyclooxygenase, and causes the symptoms of local tissue redness, swelling and heat. The drug mainly plays a role in regulating body temperature and analgesia by inhibiting the cyclooxygenase required for the synthesis of prostaglandins. [2] Because of its inhibitory effect on the synthesis of inflammatory mediators prostaglandins, it is different from aspirin, ibuprofen, etc. It mainly inhibits Central nervous system site, not in the peripheral nervous system. It is the drug of choice in patients that cannot be treated with non-steroidal anti-inflammatory drugs (NSAID), such as people with bronchial asthma, peptic ulcer disease, hemophilia, salicylate-sensitized people, children under 12 years of age, pregnant or breastfeeding women. It is recommended as a first-line treatment of pain associated with osteoarthritis.

2. Properties of the Paracetamol

2.1. Physicochemical Properties of the Paracetamol

Acetaminophen is a white crystalline powder with a molecular weight of 151.163, a boiling point of 387.8 ± 25.0 °C at 760 mmHg, and good heat resistance. In boiling water, dissolve 1 part of acetaminophen, you need 20 parts of boiling water. Other documents report solubility as 14.7 mg/ml at 20°C; 14.3 mg/ml at 25°C; 23.7 mg/ml at 37°C. Solubility is low, so acetaminophen formulations require improved solubility. Three metastable crystal forms have been reported so far. Orthorhombic is relatively stable, but the yield is low; the stable crystal forms currently commercially produced are all monoclinic.[3] There are literature reports that the measured value logP is 0.2; in other literatures, different oil-water partition coefficients are given, and the logP is 0.31. It has been reported that at 25°C, the acidic pKa of

acetaminophen is 9.5. The absolute fasting bioavailability of paracetamol reported in different literatures varies from 62% to 89%. Tmax varies from 0.17-1.2h. There are some reports in the literature that there is no effect on the absolute bioavailability of oral drugs at doses of 5-20 mg/kg.

2.2. Biopharmaceutical Properties and Adverse Reactions of Drugs

The permeability of acetaminophen is just below the cut-off for 90% absorption, although close to the BCS I class edge, acetaminophen is classified as a BCS III drug, and acetaminophen is not a narrow therapeutic window drug.

Acetaminophen is rapidly and completely absorbed by oral administration, and is evenly distributed in body fluids. The peak value is reached 0.5-2 hours after oral administration, and the effect is maintained for 3-4 hours. About 25% is bound to plasma proteins. ml) is not obviously bound to protein; the binding rate of a large amount or toxic amount to protein is high, up to 43%. 90% to 95% of acetaminophen is metabolized in the liver, about 60% is combined with glucuronic acid, and the rest is combined with sulfuric acid and cysteine. Intermediate metabolites have toxic effects on the liver. t_{1/2} is 2 to 3 hours, and can be extended by 1 to 2 times when the liver function decreases. Elderly and newborns also have lengthened, while children have shortened.[4] Acetaminophen is mainly excreted from the kidneys in the form of glucuronic acid conjugates, and about 3% is excreted in the urine in the original form within 24 hours. Under normal circumstances, it can be detoxified by binding to glutathione in the liver. When acetaminophen is used in excess, glutathione storage is depleted, and this metabolite binds to hepatocyte macromolecules, resulting in liver necrosis.

As an antipyretic and analgesic, acetaminophen is commonly used in the prescription of anti-cold medicines. In China, acetaminophen is also widely recommended for adults and children with cold fever, headache, and fever and pain caused by other diseases. This drug has been included in the Pharmacopoeia of the United States, Japan, Britain and other countries and the "Chinese Pharmacopoeia". It is one of the most widely used drugs in the world. focus on. On January 13, 2011, the U.S. Food and Drug Administration (FDA) issued measures to reduce the risk of liver damage from prescription

acetaminophen drugs, including limiting prescription) in an amount not exceeding 325 mg, and at the same time amend the instructions of such medicines to warn of the risk of liver damage and allergic reactions.

3. Determination of Route of Administration and Dosage Form

Since the common clinical use of acetaminophen is an antipyretic and analgesic drug, the preparation should have a rapid dissolution and rapid onset of action. The main dosage forms currently on the market are tablets, drops, oral liquids, suppositories, etc. The tablets include ordinary tablets, sustained-release tablets, and effervescent tablets, but for children or the elderly, due to the large differences in liver and kidney functions, Taking the same dose of drugs will lead to poor treatment effect or medication risks, especially tablets, which are usually adjusted by cutting the dose, which brings inconvenience and also causes dose errors. In severe cases, it will cause liver and kidney damage. In such a situation, individualized drug therapy is a more reasonable solution.

3.1. 3D Printing Technology

3D printing technology shows great potential in personalized drug delivery. When using 3D printing technology to prepare multi-layer dosage forms, only changing parameters in the software can achieve precise individual layer quality control, which is extremely beneficial to the development of pediatric and geriatric oral dosage forms. 3D printing technology can change the size, shape, and internal structure of the target product through computer-aided computer design. It has the advantages of accuracy and diversity.[5]It can be applied to pharmaceutical preparations to achieve individualized treatment and minimize dosing errors. A good way to make tablets.

Compound preparation is one of the important research aspects of 3D printing pharmaceutical preparations. It can not only print medicines with different doses quickly and conveniently, but also design integrated tablets with multiple independent release mechanisms according to the needs of patients, which can improve patient compliance at the same time , prolong the action time.

3.2. Hot Melt Extrusion (HME)

Hot melt extrusion technology was originally used in the plastics and rubber industries. However, since the 1970s, Hot melt extrusion has been used in pharmaceuticals because of its ability to produce extrudates with good performance, no organic solvents, and continuous processing. [6]area to gain attention. At present, HME is widely studied in the pharmaceutical field as a method for preparing solid dispersions that can improve the release rate of low-water-soluble APIs. Hot melt extrusion can not only improve its bioavailability by melt-mixing APIs with hydrophilic or water-soluble polymers, but also can be used to develop sustained-release pharmaceutical formulations with delayed drug delivery properties and masking the bitterness of APIs.

3.3. Combination Technology of Hot Melt Extrusion and Fused Deposition Printing

Fused deposition printing technology 3D printers use filamentous thermoplastic filaments. When the filament is fed into the nozzle during printing, the filament is stretched and compressed under the action of the gear, and subjected to

thermal stress that melts it. However, most of the consumables currently on the market are not suitable for pharmaceuticals, and many polymer excipients used in traditional pharmaceuticals do not have appropriate thermal and mechanical properties, which are exactly the consumables for fused deposition printing technology 3D printers. necessary.[7] Only high-quality filament filaments used in fused deposition printing technology 3D printers can produce high-quality 3D printed products. High-quality thermoplastic filaments can be efficiently produced using hot melt extrusion (HME) technology. Therefore, we chose to couple hot melt extrusion with Fused Deposition Printing.

4. Production Process

4.1. Prescription Design

To further improve the solubility of acetaminophen, I choose HPMC as the carrier. HPMC has excellent water-solubility, anti-sensitivity, inertness, stability and film-forming properties. What impressed me most about this medicine is the bitter taste, so I choose to add sucrose to increase the sweetness, so that when everyone took it, it would be less painful. Plasticizers and lubricants are added to APIs to produce high-quality thermoplastic filaments by hot melt extrusion before printing.

Prescription: acetaminophen, Sucrose, HPMC, PEG6000, 0.3% Magnesium Stearate

4.2. Preparation of Drug-loaded Printing Filament by Hot Melt Extrusion

Paracetamol, HPMC,sucrose,0.3% magnesium stearate and PEG6000 were melted and mixed in a melt extruder, the mixture was premixed in a turbo mixer at 75 r/min for 10 min, and the single screw extruder was started , preheat at 110°C, and after the temperature is stable, pour the mixed drug and polymer into the feed port of the extruder, adjust the parameters, set the screw temperature to 100°C, the extrusion temperature to 105°C, and the rotation speed to 65 r·min⁻¹ , and then extruded into filaments. Then, the wire to be printed is obtained through the processes of cooling, micro-arranging of the diameter adjuster, pulling, and winding.

4.3. Fused Deposition Printing Preparation of 3D Printed Acetaminophen Tablets

Model first and export to STL format file. The file was then imported into the Raise3D E2 3D printer with independent dual jets. [8]Printing parameters set Nozzle: 0.5 mm aperture, printing temperature: 120 ~ 140 °C, layer height: 0.7 mm, number of layers: 9 layers, printing speed: 8 ~ 12 mm/s, extrusion speed: 0.015 ~ 0.03 mm/s, Path spacing: 0.7 mm. Among them, the printing temperature is the temperature of the printing chamber during the printing process; the layer height is the distance that the nozzle rises for each layer of printing; the printing speed is the speed of the nozzle, and the extrusion speed is the speed of the piston running downward to extrude the material; the path spacing is the parallel distance between each layer of filaments.

5. Quality Evaluation

Since this method is not very popular yet and is in the developing stage, We choose method as the quality inspection method of B.S. Liu et al.[1]

a. Printing results and appearance inspection

The appearance of the tablets is compared by observation, and the standard is to obtain round, white or yellowish regular tablets.

b. Thermal stability testing and rheological research

The paracetamol was analyzed by thermogravimetric analyzer, with a temperature range of 25 to 600 °C, a heating rate of 10 °C/min, and a nitrogen flow rate of 50 m/min.

c. Investigation of crystal form and molecular structure

d. In vitro release study: USP-I method was used

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